

Appl. No. : 09/331,631
Filed : June 21, 1999

REMARKS

The pending claims of the application have been amended to more precisely define the invention, to correct errors in claims, and in connection with objections taken by the Examiner. No new matter has been added by the amendments.

With regard to the amendment of part (d) of claim 16, this is based, *inter alia*, on the Example 11 disclosure where there is specific mention of the testing of purified proteins for antimicrobial activity (see page 26, lines 11-13 of the published PCT pamphlet). The feature of testing the activity of the protein prepared by the recited method is also recited in present claim 42. The amendment in no way, therefore, constitutes the introduction of new matter.

Claim 42 has been cancelled, being redundant on claim 16 as amended.

Claims 44 and 45 have been amended to recite that "X is any amino acid residue other than cysteine" for consistency with the qualifying addition previously made to claim 1.

Claim 46 has been amended to begin the claim with the recitation "A composition..."

The changes made to the claims by the foregoing amendments are shown herein, including ~~deletions~~ and additions, are shown are shown herein with deletions designated with a strikethrough and additions underlined. No new matter has been added herewith.

I. Status of the claims

Applicants acknowledge that claims 1-3, 11-21, 30, 31, 34, 36, 37, and 39-54, are pending in the application.

Applicants also acknowledge that claims 12, 14, 15, 34, 36, 37, 39, and 40, have been withdrawn from consideration.

With regard to claims 12, 14, 15, 36, 37, 39 and 40, Applicants again remind the Examiner that in the response to Paper No. 5, rejoinder of the Group III claims was requested upon allowance of the Group I claims and claim 1 in particular. Each of claims 12, 14, 36, 37, 39 and 40 is dependent, either directly or indirectly, on claim 1 and relate to pharmaceutical compositions comprising the antimicrobial proteins of the invention, or methods of using the antimicrobial proteins on mammals. Applicants note that claim 31 as amended by the response to Paper No. 12 has been rejoined. This claim is directed to a composition comprising a protein fragment of an antecedent claim together with a pharmaceutically-acceptable carrier diluent or excipient. Applicants respectfully submit that rejoinder of claims 12, 14, 36, 37, 39 and 40 is warranted in view of the rejoinder of claim 31.

Appl. No. : 09/331,631
Filed : June 21, 1999

Concerning claim 34, this was withdrawn from consideration following amendment made as part of a response to Paper No. 10. An amendment made to the claim in Paper No. 14 brought the claim into conformity with other Group I method claims such as claim 13. However, claim 34 still stands withdrawn. Applicants respectfully request that it be examined during the Examiner's consideration of the present response.

II. Objections and rejections concerning the phrase "...other than cysteine..."

As with previous Office Actions, the core issue in the present Action is the recitation sought to be added to the description and claims that "X is any amino acid residue other than cysteine". This issue has been discussed at length in previous responses and in Paper No. 18 in particular. Since most of the matters raised in the present Action relate to this issue, it will again be addressed in general terms before commenting on the specific matters.

In paragraph 10 of the present Action, the Examiner states that argument submitted in the previous response "is not persuasive because applicant is essentially asking one skilled in the art to insert information that is not written in the disclosure in *[sic]* to provide support for the claims". The Examiner then supports this position with the following:

"The statement made on page 9 of the [previous] response is very clear "[A]pplicants do not deny that there is an absence of such an explicit recitation in the description".

How then can absence of information be interpreted as applicants had possession of the claimed subject matter."

Applicants respectfully submit that the Examiner has misinterpreted the quoted passage as an admission that the "X is any amino acid residue other than cysteine" feature is not included in the description.

The admission intended in the quoted passage was that the specific words "X is any amino acid residue other than cysteine" were not present in the description as filed. However, in no way was this an admission that the information was not present. Specific words are not necessary to include information. What must be considered is the disclosure as a whole.

Applicants have elaborated at length in previous responses on the nature of the invention and what was disclosed in the application as filed in the context of that invention. In summary, the invention resides in the provision of proteins with antimicrobial activity. A distinct feature of these proteins is a particular spacing of cysteine residues. It is made abundantly clear throughout

Appl. No. : 09/331,631
Filed : June 21, 1999

the description that the cysteine spacing is a crucial aspect of the invention and this has not changed since the application was filed.

At pages 8 and 9 of the previous response, there is a listing of references in the description to the specific cysteine spacing of the subject polypeptides. These references were present in the application as filed. Mention was also made in a previous response to the drawings (as filed) which, in Figure 4, comprise an alignment of sequences. In not one sequence is there an occurrence of a cysteine residue other than in accordance with the specified spacing of such residues.

Reference is also made to the following passages in the response filed April 4, 2002 to Paper No. 12:

“A key recitation [in claim 1] is that the polypeptide has a particular spacing of cysteine residues. This spacing is specified in the formula “C-2X-C-3X-C-(10-12)X-C-3X-C-3-C”. Thus, if any X is a cysteine, the spacing of this residue will not be as specified in the formula.

It is thus a fundamental aspect of the claim as originally drafted that the X of the formula C-2X-C-3X-C-(10-12)X-C-3X-C-3X-C (SEQ ID Nos: 37-39) is any amino acid residue with the exclusion of cysteine.”

In view of the foregoing, Applicants unreservedly reject the Examiner’s assertion that they were not in possession of the invention prior to the amendment under discussion.

Applicants also unreservedly reject the Examiner’s contention that we are “essentially asking one skilled in the art to insert information that is not written in the disclosure”. How can information be inserted that is already there?

All that is sought by the amendment is to make it abundantly clear to all addressees of the specification—including those with less than ordinary skill in the art—that the X residue in the formula C-2X-C-3X-C-nX-C-3X-C-3X-C is any residue other than cysteine. As noted in the response filed April 4, 2002, it was not necessary for this amendment to be made to claim 1—and subsequently elsewhere—but it was done purely for clarity.

The Examiner also comments in paragraph 10 of the present Action on the ‘Support for “X is any amino acid other than cysteine”’ sub-section of the previous response. The Examiner states that “X is any amino acid other than cysteine” is not accurate since ““X” is any amino acid” can produce the following result: “C-2X-C-3X-C...” can be equivalent to “C-A-C-DDDC” or

Appl. No. : 09/331,631
Filed : June 21, 1999

“C-AA-DDD-C...” etc.’ Applicants are puzzled as to the point of this passage as in none of the examples is there a “C-2X-C-3X-C...” spacing. If the Examiner’s intention was to give as an example the sequence “C-AA-C-DDD-C...”, this conforms to the requirement that the initial portion of the protein according to the invention has the sequence “C-2X-C-3X-C...” where X is any amino acid residue other than cysteine.

The Examiner further comments that ‘[t]he proviso “X” is any amino acid, does not mean that every appearance of “X”, has a “cysteine” residue’. Applicants do not dispute this and in the previous response an example was given, viz:

C-3X-C-3X-C-3X-C-2X-oX-C-3X-C

of a portion of the claim 1 sequence where every X is not C. However, since some of the X residues of the partial claim 1 sequence have been made cysteines, the specific cysteine spacing of C-3X-C-nX-C-3X-C has been destroyed. To attain the proteins of the invention, X can be any amino acid residue with the exception of cysteine. This has been an explicit aspect of the specification since filing. The amendment to include the words “other than cysteine” in the definition merely constituted an introduction of an implicit recitation but in no way constituted the addition of new matter.

The Examiner comments in paragraph 10 at the middle of page 8 of the Action that “[w]hat is disclosed or recited is what is considered during examination ...”. Applicants implore the Examiner to do precisely that. At no time has the Examiner acknowledged what is disclosed and recited as the invention. Specifically, proteins with a particular spacing of cysteine residues. Instead, the Examiner has chosen to focus on words—not information—which were not initially used in connection with matter included in the application as filed.

Applicants believe that they have clearly shown in this and previous responses that there has always been disclosure and recitation of proteins with a specific spacing of cysteine residues which can only be maintained if the intervening residues are other than cysteine. The Examiner is accordingly urged to withdraw those objections and rejections which relate to the phrase “... other than cysteine ...”.

III. Objection to the Specification

In paragraph 4 of the Action, the Examiner has objected to the specification as failing to provide proper antecedent basis for the claimed subject matter. The Examiner contends that

Appl. No. : 09/331,631
Filed : June 21, 1999

there is no support in the original disclosure for the recitation in claim 1 that "X is any amino acid residue other than cysteine" and for the inclusion of this recitation in the specification. For the reasons given in the previous section of this paper and in previous responses, Applicants respectfully point out that the recitation is supported by the original disclosure. Accordingly, Applicants respectfully request that the objection be withdrawn.

In paragraph 5 of the Action, the Examiner has called for cancellation of what she considers to be material added to claim 1. The Examiner contends that the amendment of claim 1 to read "X is any amino acid residue other than cysteine" is not supported by the description where it is stated at pages 4 and 10 that "X is any amino acid residue".

Applicants submit that the passage "X is any amino acid residue" must be read in the context of the disclosure as a whole. As discussed above in the introductory comments section and in the previous response, there is disclosure of a specific cysteine spacing in the polypeptides the subject of the instant application. To interpret the foregoing passage as meaning that X can be any amino acid residue including cysteine completely nullifies the specified spacing.

To maintain the specified cysteine spacing in the subject polypeptides, X cannot be cysteine. As discussed at length above, there is, therefore, implicit disclosure of X being any amino acid residue other than cysteine and there is accordingly support for the amendment to claim 1. Applicants therefore respectfully submit that there is no need for cancellation of the material added to claim 1 by the subject amendment.

IV. Rejection under 35 U.S.C. §112, first paragraph

The Examiner has rejected claims 1-3, 11, 13, 16-21, 30, 31 and 41-54 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in such a way as to reasonably convey to one of skill in the art that the inventors, at the time the application was made, had possession of the claimed invention.

With regard to claim 1 and claims dependent thereon, the Examiner asserts that new matter has been added to the first-mentioned claim by the recitation that "X is any amino acid residue other than cysteine". In a reiteration of objections taken under other grounds, the Examiner asserts that the specification provides no support for this amendment because it is disclosed therein that "X is any amino acid residue".

Appl. No. : 09/331,631
Filed : June 21, 1999

Applicants reiterate yet again that the passage "X is any amino acid residue" should not be read in isolation. As discussed above, when the description is considered as a whole, particularly the passages dealing with the cysteine spacing of the subject polypeptides, it is clear that the passage must be read as "X is any amino acid residue other than cysteine".

One skilled in the relevant art on reading the description would immediately appreciate that a particular cysteine spacing is necessary in a polypeptide for it to have the antimicrobial activity of the polypeptides the subject of the instant application. That skilled person would also appreciate that the inclusion of cysteine as an X residue would destroy the specified spacing of cysteine residues. The skilled person would thus intuitively read into "X is any amino acid residue" the additional words "other than cysteine".

As evidence of how a person of skill in the art would read the passage "X is any amino acid residue", Applicants once more refer the Examiner to the declaration by Dr Donald Maclean which accompanied the response filed April 4, 2002 to Paper No. 14. In particular, we draw the Examiner's attention to paragraph 6 of the Maclean declaration where the following is stated:

'In my opinion, therefore, it is implicit within the passage that "X is any amino acid residue" must be read as "X is any amino acid residue other than cysteine".'

Applicants submit that the subject matter of claim 1 and dependent claims was described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the invention at the time the application was made.

In connection with claim 16, the Examiner asserts that the invention has not been adequately described because claim 16 requires a search of a database using 'an unspecified/unknown algorithm' to identify an amino acid sequence in the claimed method and there is no indication as to what sequence; what algorithm; what database is to be employed to identify this sequence'. Applicants respectfully point out that there is clear instruction in the specification as to how to carry out the claimed method. In any case, one of ordinary skill in the art would be cognizant of the algorithms appropriate for the required identification. As to the sequence, this may be any sequence in any database available to the person of skill in the art. That person would have immediate knowledge of such databases and have access thereto.

With regard to the matter raised by the Examiner in paragraph 6 at the bottom of page 4 of the Action, claim 16 has been amended to recite in part (d) the additional step of testing for

Appl. No. : 09/331,631
Filed : June 21, 1999

antimicrobial activity. As a consequence of this step, a protein with such activity can result from the method defined in the claim.

In view of the foregoing comments and relevant claim amendments, Applicants submit that withdrawal of the 35 U.S.C. 112, first paragraph, rejection of claims 1-3, 11, 13, 16-21, 30, 31 and 41-54 is warranted.

V. Rejection under 35 U.S.C. §112, second paragraph

In paragraph 7 of the Action, the Examiner has rejected claims 1-2, 11, 13, 16-18, 20-21, 41-42, 46, 48, 50-51 and 53 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

With regard to claims 1, 2, 11, 13 and 17-21, the Examiner asserts that there is no support in the specification for the phrase “X is any amino acid other than cysteine” recited in at least claim 1. As discussed elsewhere in this response, the “other than cysteine” recitation is fully supported by the description and an amendment has furthermore been made to include a specific recitation to the foregoing effect in the description. Since there is support for the “other than cysteine” recitation in the description there is an antecedent basis in claims 1, 2, 11, 13 and 17-21 for the phrase referred to by the Examiner.

The Examiner has rejected claim 13 as being indefinite because the claim is a method claim which improperly depends from a product claim. While not agreeing with this assertion, Applicants have amended claim 13 as suggested by the Examiner in paragraph 10 of the Action.

The Examiner further asserts that claim 16 is indefinite ‘because of the recitation of “an unspecified/unknown algorithm to be used to identify or design an amino acid sequence” as the metes and bounds of the method is [sic] not defined’. The metes and bounds of the claim with regard to the foregoing aspects would be readily and fully apparent to one of even modest skill in the art. Furthermore, the specification provides direction in at least Example 8 as to how the method can be performed. Applicants thus respectfully submit that the Examiner’s rejection of the claim has not been made out.

Claim 46 has been amended in connection with the matter raised at the top of page 6 of the Action.

Appl. No. : 09/331,631
Filed : June 21, 1999

In the light of the above comments and the relevant claim amendments, Applicants submit the withdrawal of the 35 U.S.C. 112, second paragraph, rejection of claims 1-2, 11, 13, 16-18, 20-21, 41-42, 46, 48, 50-51 and 53 is called for.

VI. Rejection under 35 U.S.C. §102(a)

In paragraph 8 of the instant Action, the Examiner has maintained the rejection of claim 1 under 35 U.S.C. 102(a) as being anticipated by Tartar *et al.* (EP 0 093 652). The basis of the rejection is that the citation discloses peptides used to vaccinate against *E. coli* enterotoxins and the sequence contained in SEQ ID No: 39 with the formula C3XC12XC3XC wherein X is any amino acid residue and C is cysteine.

Applicants reiterate the argument presented in previous responses that the rejection based on Tartar *et al.* can only hold if X as defined in claim 1 can be any amino acid residue. However, in the light of what is described as the invention and particularly in the light of claim 1 as amended, X is any amino acid residue other than cysteine.

With cysteine excluded as an X residue, the Tartar *et al.* sequence of CELCCNPACAGCYNTFYCCELC no longer falls within the formula C3XC12XC3XC. To do so, the Tartar *et al.* sequence would have to be CEL*CNPA*AG*YNTFYC*ELC where each asterisk denotes a residue other than cysteine. This would be a vastly different sequence to that actually disclosed.

Applicants have once more pointed out above that there is support in the description for the "other than cysteine" qualification in the definition of X. Consequently, the amendment to include this qualification in the claim should be allowed. However, as argued elsewhere (see Paper No. 14), the definition of X without the qualification inherently excludes cysteine in view of the specified cysteine spacing.

Since the Tartar *et al.* sequence does not fall within the scope of claim 1 when the proper definition of X is applied, the citation is not an anticipation. Accordingly, Applicants respectfully request that the 35 U.S.C. 102(a) rejection of claim 1 on the basis of Tartar *et al.* be withdrawn.

In paragraph 11 of the Action, the Examiner has maintained the rejection of claim 1 under 35 U.S.C. 102(a) as being anticipated by Voerman (WO 96/13585). The Examiner states that

Appl. No. : 09/331,631
Filed : June 21, 1999

Voerman discloses the sequence contained in SEQ ID No: 37 "with 100% sequence identity where the sequence is C3XC10XC3XC".

The formula of amended claim 1, there are 11 or 12 X residues between the two C3XC motifs. The Voerman sequence has 10 X residues between the motifs. Consequently, claim 1 as amended is not anticipated by Voerman. Applicants therefore respectfully request that the rejection of claim 1 under 35 U.S.C. 102(a) be withdrawn.

Conclusion

Should there be any further questions regarding the above-captioned patent application, the Examiner is respectfully requested to contact the undersigned attorney at the telephone number below. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 10/3/03

By: Sanjivpal S. Gill
Sanjivpal S. Gill
Registration No. 42,578
Attorney of Record
Customer No. 20,995
(415) 954-4114

W:\DOCS\JAHJAH-6737.DOC
100103